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07/30/02 → 08/01/01

CLAIMS:

1. A 38-residue CRFR1 ligand peptide which binds to CRFR1 with an affinity substantially greater than it binds to CRFR2, which peptide has the following formula, or a nontoxic salt thereof:

Y_1 -Pro-Pro- R_6 -Ser- R_8 -Asp- R_{10} - R_{11} -D-Phe- R_{13} - R_{14} - R_{15} -Arg- R_{17} - R_{18} - R_{19} - R_{20} - R_{21} - R_{22} - R_{23} - R_{24} - R_{25} - R_{26} - R_{27} - R_{28} - R_{29} -Gln-Glu- R_{32} - R_{33} - R_{34} -Arg- R_{36} - R_{37} - R_{38} - R_{39} - R_{40} - R_{41} -NH₂ wherein Y_1 is an acyl group having not more than 15 carbon atoms or is radioiodinated tyrosine; R_6 is Ile, Met or Nle; R_8 is Leu or Ile; R_{10} is Leu or CML; R_{11} is Thr or Ser; R_{13} is His, Tyr or Glu; R_{14} is CML or Leu; R_{15} is CML or Leu; R_{17} is Glu, CML, Asn or Lys; R_{18} is Val, CML, Nle or Met; R_{19} is CML, Leu or Ile; R_{20} is Glu, D-Glu or His; R_{21} is Nle, Leu, CML or Met; R_{22} is Ala, D-Ala, Aib, Thr, Asp or Glu; R_{23} is Arg or Lys; R_{24} is Ala, Gln, Ile, Asn, CML or Aib; R_{25} is Asp or Glu; R_{26} is Gln, Asn or Lys; R_{27} is CML, Glu, Gln or Leu; R_{28} is Ala, Lys, Arg or Aib; R_{29} is Gln, Aib or Glu; R_{32} is Aib or an L- or D-isomer of a natural α -amino acid other than Cys; R_{33} is Aib or an L- or D-isomer of Ser, Asn, Leu, Ala, CML or Ile; R_{34} is Lys or Orn; R_{36} is Lys, Orn, Arg, Har, CML or Leu; R_{37} is CML, Leu, Nle or Tyr; R_{38} is Nle, Met, CML or Leu; R_{39} is Glu, Aib or Asp; R_{40} is Ile, Aib, CML, Thr, Glu, Ala, Val, Leu, Nle, Phe, Nva, Gly or Gln; and R_{41} is Ala, Aib, Ile, CML, Gly, Val, Leu, Nle, Phe, Nva or Gln; provided that a cyclizing bond may exist between Glu in position 31 and R_{34} and provided further that D-2Nal or D-Leu may be substituted for D-Phe.

abbreviations
check

2. A peptide according to claim 1 having the formula:

(cyclo 31-34) Y_1 -Pro-Pro- R_6 -Ser- R_8 -Asp-Leu- R_{11} -D-Phe-His- R_{14} -Leu-Arg-Glu- R_{18} -Leu- R_{20} -Nle- R_{22} - R_{23} -Ala- R_{25} -Gln-Leu-Ala- R_{29} -Gln-Glu- R_{32} - R_{33} - R_{34} -Arg- R_{36} - R_{37} -Nle- R_{39} - R_{40} - R_{41} -NH₂ wherein Y_1 is an acyl group having not more than 7 carbon atoms; R_{20} is Glu or D-Glu; R_{22} is Ala or Thr; R_{29} is Gln or Glu; R_{32} is His, Aib, Ala, Gly, Leu, Gln or Glu; R_{36} is Lys or Leu; R_{37} is Leu or CML; R_{39} is Glu or Asp; R_{40} is Ile, CML or Glu; and R_{41} is Ile, Aib or Ala; with the remaining variables being as defined in claim 2.

3. A peptide according to claim 1 having the formula:

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-Leu-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Glu-Ile-Ile-NH₂, or

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Glu-Ile-CML-NH₂; or

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-Aib-Lys-Arg-Lys-Leu-Nle-Glu-Ile-CML-NH₂.

4. A peptide according to claim 1 having the formula:

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-Leu-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Glu-Ile-Ile-NH₂, or

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Glu-Ile-CML-NH₂; or

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-Aib-Lys-Arg-Lys-Leu-Nle-Glu-Ile-CML-NH₂.

duplicate

5. A CRF according to claim 1 having the formula:

Y₁-Pro-Pro-R₆-Ser-R₈-Asp-Leu-R₁₁-D-Phe-His-R₁₄-Leu-Arg-Glu-R₁₈-Leu-R₂₀-Nle-R₂₂-R₂₃-Ala-R₂₅-Gln-Leu-Ala-R₂₉-Gln-Glu-R₃₂-R₃₃-R₃₄-Arg-R₃₆-R₃₇-Nle-R₃₉-R₄₀-R₄₁-NH₂ wherein Y₁ is an acyl group having not more than 7 carbon atoms; R₂₀ is Glu or D-Glu; R₂₂ is Ala or Thr; R₂₃ is Arg or Lys; R₂₉ is Gln or Glu; R₃₂ is His, D-His, Aib or Ala; R₃₆ is Lys or Leu; R₃₇ is Leu or CML; R₃₉ is Glu or Asp; R₄₀ is Ile, CML or Glu; and R₄₁ is Ile, Aib or Ala; wherein the remaining variables are as defined in claim 2 and wherein the side chains of (Glu³¹) and R₃₄ may be covalently connected.

R₃₁ = Glu

6. A peptide according to claim 1 wherein R₁₈ is Val, R₂₂ is Ala, R₂₃ is Arg, R₂₄ is Ala, R₂₅ is Glu, R₂₉ is Ala, R₃₉ is Glu, and R₄₁ is Ile.

7. A peptide according to claim 1 having the following formula, or a nontoxic salt thereof:

(cyclo 31-34)Y₁-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-R₂₂-R₂₃-Ala-Glu-Gln-R₂₇-Ala-Gln-Gln-Glu-R₃₂-R₃₃-Lys-Arg-Lys-Leu-

Nle-Glu-R₄₀-Ile-NH₂, wherein R₂₂ is Ala or Thr; R₂₇ is Leu or CML; R₃₂ is His or Aib; R₃₃ is Ser or Aib; and R₄₀ is Ile or CML.

8. A peptide according to claim 1 having the formula:

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-Leu-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Glu-Ile-Ile-NH₂, or

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-Ser-Lys-Arg-Lys-Leu-Nle-Glu-Ile-CML-NH₂; or

(cyclo 31-34)Ac-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-D-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Nle-Ala-Arg-Ala-Glu-Gln-CML-Ala-Gln-Gln-Glu-His-Aib-Lys-Arg-Lys-Leu-Nle-Glu-Ile-CML-NH₂.

3, 1, 8.

duplicate

9. A peptide according to claim 1 which is useful as a tracer that selectively bonds to CRFR1 wherein Y is radioiodinated D-Tyr or L-Tyr.

lack of antecedent.

10. A 38-residue CRFR1 ligand peptide which binds to CRFR1 with an affinity substantially greater than it binds to CRFR2, which peptide has the formula Y₁-Pro-Pro-A-D-Xaa-B-Glu-Xaa₆-Xaa₆-Xaa₆-C-NH₂, wherein Y₁ is an acyl group having not more than 15 carbon atoms or is radioiodinated tyrosine; A is a sequence of 6 amino acid residues that is found between Pro in the 5-position and Phe in the 12-position of r/hCRF or the corresponding sequence of another peptide of the CRF family; D-Xaa is D-Phe, D-2Nal or D-Leu; B is a sequence of 18 amino acid residues that is found between Phe in the 12-position and Ala in position-31 of r/hCRF or the corresponding sequence of another peptide of the CRF family; Xaa₆ is any L- or D-natural α -amino acid other than Cys or is Aib; Xaa₆ is Aib or an L- or D-isomer of Ser, Asn, Leu, Ala, CML or Ile; Xaa₆ is either Lys or Orn, the side chain of which may be linked in an amide cyclizing bond to that of Glu; and C is a sequence of the last 7 amino acid residues of the C-terminal portion of any peptide of the CRF family; provided that Nle or Leu may be substituted for Met in A, B and/or in C.